REMARKS/ARGUMENTS

Applicants have carefully considered the Examiner's comments set forth in the Office Action of April 26, 2011 and respectfully request reconsideration of the above-identified application in view of the following remarks.

Claims 1 to 12, 15 and 16 remain pending in this application. Claims 3, 5, 6 and 10 to 12 are withdrawn from consideration as being drawn to a non-elected invention and species. Claims 13, 14 and 17 to 25 have been cancelled. Claims 2, 8, 15 and 16 have been amended to further define and clarify Applicant's invention. Claim 12 has been amended to correct a typographical error. No new subject matter has been added.

The Office Action

Claim Rejections - 35 U.S.C. § 112

Claim 14 was rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicant respectfully disagrees with the Examiner's rejection. However, without acquiescing to the Examiner's rejection and in order to advance the prosecution of the present application, Applicant has cancelled Claim 14 without prejudice or disclaimer and as such, the Examiner's rejection of this claim under 35 U.S.C. § 112, first paragraph, has been rendered *moot*.

Claim Rejections - 35 U.S.C. § 102(b)

Claims 1, 2, 4 and 14 to 16 were rejected under 35 U.S.C. § 102(b) as being anticipated by the Feng publication (1998) (Feng *et al.*) and by King *et al.* (US 6,339,075). Claims 1, 2, 4, 7 to 9 and 14 to 16 were also rejected under 35 U.S.C. § 102(b) as being anticipated by Edwards *et al.* (CA 2,483,917). As discussed above, Applicant has cancelled Claim 14 without prejudice or disclaimer and as such, the Examiner's rejection of this claim under 35 U.S.C. § 102(b), has been rendered *moot*. With respect to the Examiner's rejections of Claims 1, 2, 4, 15 and 16 under 35 U.S.C. § 102(b), Applicant respectfully disagrees. In particular, independent Claim 1 of the present application claims a method of enhancing mucus function comprising administering an effective amount of a mucothickening agent to a subject in need thereof. The description of the present application teaches that in one aspect of the present invention, enhancing of mucus function is for reducing the amount of aerosolization. The description of the present application

also teaches in paragraph [0043] that the term "mucothickening agent" means a mucomodulator designed or intended to produce a thicker mucus. The description of the present application further teaches in paragraph [0042] that the term "mucomodulator" means an agent designed or intended to produce mucomodulation of mucus, for example, but not limited, to enhance the clearance of mucus from the respiratory system and/or optimize aspects of lung defense that depend on the mucus layer. Moreover, the description of the present application teaches in paragraph [0041] that the term "mucomodulation" means modifying the physical properties of mucus (viscoelasticity, cohesivity, surface tension) by altering the viscosity and/or elasticity. Furthermore, the description of the present application teaches in paragraph [0044] that the term "thick" means viscous and/or elastic and/or rigid, in reference to the physical properties of mucus and that in more scientific terms, "thick" means of high modulus of viscoelasticity (the capacity to deform and flow under applied pressure).

The Examiner asserts that Feng *et al.* disclose enhancing mucus function by administering a mucothickening agent, dextran. The Examiner also asserts that King *et al.* disclose a method of enhancing mucus function comprising administering an effective amount of a mucothickening agent. Applicant respectfully disagrees with the Examiner's assertions. In particular, both Feng *et al.* and King *et al.* disclose the use of Dextran 4000; a low molecular weight (LMW) dextran. Feng *et al.* disclose that Dextran 4000 reduced the viscoelasticity, crosslink density and cohesiveness of mucus. King *et al.* disclose that Dextran 4000 decreases mucus spinnability and viscoelasticity. King *et al.* also disclose that the mechanism for the decrease in viscoelasticity with LMW dextran administration is believed to be due to the substitution of oligosaccharide moieties occupying hydrogen bonding sites linked to the high molecular weight mucin peptides that make up the mucus gel by dextran moieties. King *et al.* further disclose that the new mucin-dextran hydrogen bonds form structurally and rheologically ineffective crosslinks because of the relatively small length of the LMW dextran polymer, thus reducing the overall crosslink density.

As such, LMW dextran would be understood by persons skilled in the art to be a mucolytic agent since it serves to reduce mucin gel crosslinking by disrupting intermolecular mucin-mucin H-bond crosslinks, substituting instead mucin-dextran crosslinks which are dysfunctional for network formation.

The mucus macromolecule consists of a protein core surrounded by short oligosaccharide side-chains, held together by different links: O-glycosidic bonds, disulphide bridges, hydrogen

bonds and ionic bonds. These links are the targets of the existing mucolytic agents. The bonds that keep mucus together and effect viscoelasticity are depicted in FIG. 1 of the present application and include: covalent bonds, ionic bonds, van der Waals' forces, intermingling, and extracellular DNA & F-Actin.

Breaking covalent bonds with mucolytic agents reduces mucin molecular weight and results in decreased mucus viscoelasticity. On the contrary, the mucothickening agents of the present invention do the opposite of what mucolytic agents do (*i.e.*, reverse mycolysis). In particular, the mucothickening agents of the present invention promote the formation of one or more of covalent bonds, ionic bonds, hydrogen bonds, van der Waals' forces, intermingling or extracellular DNA & F-actin network, in mucus. In this aspect, the mucothickening agents of the present invention reduce the aerosolizability of respiratory secretions while maintaining mucociliary clearability, and thus normal airway clearance function. This requires more subtle manipulation of mucus viscosity and elastic properties than conventional mucolytic therapies offer. The mucothickening agents of the present invention disrupt ionic and/or hydrogen bonds. This produces more subtle effects on viscoelasticity, since only side-chain interactions are affected. The approaches include increasing ionic interactions by adding divalent cations, increasing specific interactions between side chain sugars, as with sodium tetraborate or other tetrafunctional anions which will selectively crosslink galactose units, and increasing H-bond crosslinking with agents like HMW dextran or other HMW polysaccharides. By increasing the crosslinking binding sites in the mucin glycoprotein gel network, mucin gel viscoelasticity is thereby raised and/or poorly soluble mucin complexes are formed. The result is a less aerosolizable respiratory secretion, which decreases the degree of contagiousness.

In an embodiment of the present invention, the mucothickening agent is a HMW polysaccharide, such as HMW dextran or a pharmaceutically acceptable salt thereof. The description of the present application teaches in paragraph [0047] that HMW dextran means mean molecular weight ca. 70,000 Daltons or greater, more suitably in the range of 100,000-1,000,000 Daltons, as assayed by conventional viscometric techniques. The HMW dextran has approximately the same molecular weight as the subunits of mucin macromolecules; in this case mucin-dextran crosslinks are approximately as effective as the original mucin-mucin crosslinks (see FIG. 2 of the present application). HMW dextran raises elasticity relative to viscosity (as indicated by the increase in spinnability relative to log G^*), thus its use would tend to inhibit aerosolizability,

which will depend on spinnability, while maintaining mucociliary clearability. Surprisingly, it has been found to also improve or increase respiratory tract mucus cough clearability.

HMW dextran, as evidenced from FIG. 2 of the present application, would not be considered by persons skilled in the art to be a mucolytic agent. In particular, as disclosed in Example 1 of the present application, HMW dextrans show interesting effects in terms of predicted mucociliary and cough clearance. A reduction in log G* at 1 rad/s (upper graph) is a primary predictor of improved mucociliary clearability (FIG. 2A), while a reduction in spinnability (FIG. 2B) predicts improved cough clearability. The data indicate that at some intermediate to high molecular weight level (>70,000 Daltons), there will be a dextran fraction where log G* is reduced while spinnability is increased, which will differentially affect cough and mucociliary clearability. This HMW dextran fraction produces the desired combination of reduced cough aerosol clearance while maintaining mucociliary clearance function. Further, as shown in Example 5 of the present application, HMW dextran decreases cough aerosol formation while increasing "expectoration" (bulk mucus transport).

Edwards *et al.* disclose formulations for pulmonary administration including a material that significantly alters physical properties, such as surface tension, surface elasticity and bulk elasticity, of lung mucus lining fluid, which may be a surfactant and, optionally, a carrier. Edwards *et al.* also disclose that the formulation is administered preferably prior to or shortly after infection, to decrease or prevent infection and then viral shedding, in an amount sufficient to decrease surface instabilities in the liquid lining the airways of the lung, *i.e.*, to damp the rate of droplet formation from lung fluid. Edwards *et al.* further disclose that the material that significantly alters physical properties of lung mucus lining fluid is administered in an amount to increase surface elasticity and alter surface tension within the lung. The Examiner asserts that Edwards *et al.* disclose an example showing that using 50K Da dextran can also significantly reduce aerosolization (decreasing aerosolization) and as such, Edwards *et al.* meet all the limitations of the claims and thereby anticipate the claims. Applicant respectfully disagrees with the Examiner's assertion. In particular, in the example referred to by the Examiner, Example 2 of Edwards *et al.*, one of the solutions contained 20/80 ethanol/water and 3.75 g/L of 50K Da dextran. 50K Da dextran is a LMW dextran which would be understood by persons skilled in the art to be a mucolytic agent and not a mucothickening agent; an element of independent Claim 1 of the present application. Another solution contained a combination of 20/80 ethanol/water and 3.75 g/L of 500K Da dextran. This

combination would not be considered by persons skilled in the art to be a mucothickening agent; an element of independent Claim 1 of the present application. In addition, as shown in Figure 8 of Edwards *et al.*, the solution containing a combination of 20/80 ethanol/water and 3.75 g/L of 500K Da dextran resulted in the most fluorescence reaching the filter whereas the solution containing 20/80 ethanol/water only yielded less aerosol deposition on the filter than that observed for the pure water solution, indicating that ethanol/water alone alters the lung lining fluid in such a way that it can lead to less aerosol emitting therefrom. These results indicate that the addition of 3.75 g/L of 500K Da dextran to the 20/80 ethanol/water changed the bulk fluid properties too dramatically leading to greater aerosol emission; an undesirable result in a method for limiting infectivity and transmission of airborne diseases. On the contrary, independent Claim 1 of the present application is directed to enhancing mucus function, which would be understood by persons skilled in the art to mean, in one embodiment, a reduction in the amount of aerosolization. As such, Edwards *et al.* does not disclose each and every element of independent Claim 1 nor does it enable the subject matter claimed therein.

Thus, for at least all of the reasons above, none of Feng *et al.*, King *et al.* or Edwards *et al.* disclose or enable a method of enhancing mucus function comprising administering an effective amount of a mucothickening agent to a subject in need thereof as claimed in independent Claim 1 of the present application. Since there is no disclosure or enablement in Feng *et al.*, King *et al.* or Edwards *et al.* of each and every element of independent Claim 1 of the present application, this claim, as well as the claims that are dependent thereon, are distinguishable over and above Feng *et al.*, King *et al.* and Edwards *et al.* and cannot be anticipated thereby. Therefore, in view of the arguments presented herein, Applicant respectfully submits that it has overcome the Examiner's rejection of Claims 1, 2, 4, 15 and 16 under 35 U.S.C. § 102(b) as being anticipated by Feng *et al.*, King *et al.* and Edwards *et al.*, and respectfully requests favourable reconsideration thereof.

CONCLUSION

For the reasons detailed above, it is submitted all remaining claims (Claims 1, 2, 4, 7 to 9, 15 and 16) are now in condition for allowance. An early notice to that effect is therefore earnestly solicited.

☒ This is an authorization under 37 CFR 1.136(a)(3) to treat any concurrent or future reply, requiring a petition for extension of time, as incorporating a petition for the appropriate extension of time.

☒ The Commissioner is hereby authorized to charge any filing or prosecution fees which may be required, under 37 CFR 1.16, 1.17, and 1.21 (but not 1.18), or to credit any overpayment, to Deposit Account 192253.

In the event the Examiner considers personal contact advantageous to the disposition of this case, he/she is hereby authorized to call Kitt Sinden, at Telephone Number (416) 849-8457.

Respectfully submitted,

SIM & MCBURNEY

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Date

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